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Remarks

Claims 1, 15, 51, 66 and 81-151 are pending in the subject application. By this Amendment, Applicants have canceled claims 2-14, 16-50, 52-65 and 67-80 and added claims 81-151; claims 1, 15, 51, and 66 are withdrawn from consideration. Support for the new claims can be found throughout the subject specification and in the claims as originally filed (*see*, for example, pages 24-28 and pages 32-55). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1, 15, 51, 66, and 81-151 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

In the previous Office Action, claims 46-47 were objected to as being a substantial duplicate of claims 36-37. Claims 36-37 and 46-47 are canceled thereby making the objection moot. As such, Applicants respectfully request the objection be reconsidered and withdrawn.

Claims 29-34, 36-44 and 46-50 were rejected in the previous Office Action under 35 U.S.C. § 112, second paragraph as allegedly being indefinite because the term "disease causing substance" is not defined with any chemical or physical characteristics. In response, Applicant respectfully submits that paragraph 5.1.2 (at page 25 or paragraph 0145 of the published application) clearly defines the term "disease causing substance":

> As used herein, the term "disease-causing substance" means any solid, semisolid, paste, gel, plaque, or liquid in dissolved or undissolved form, that can crystalize, precipitate, or otherwise accumulate or deposit in solid form in an animal body, thereby causing or aggravating a disease process. Examples of disease-causing substances include, but are not limited to, calcium salts and compositions thereof, such as calcium phosphate, calcium carbonate, calcium pyrophosphate, brushite, apatite, hydroxyapatite, calcium oxalate, kidney stones, and bone tissue; magnesium salts and compositions thereof, such as magnesium ammonium phosphate; uric acid and salts thereof; cholesterol and cholesterol compositions, such as cholesterol gall stones; bilirubin, salts thereof, and compositions thereof, such as pigment gall stones; or hydrates and mixtures thereof; tooth plaque; dental calculus; and protein precipitates, such as amyloid protein deposits.

The test for definiteness under 35 U.S.C. § 112, second paragraph is whether "those skilled in the art would understand what is claimed when the claim is read in light of the

specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). Thus, if one skilled in the art is able to ascertain the meaning of the term "disease-causing substance" in light of the specification, the requirements of 35 U.S.C. § 112, second paragraph are satisfied.

Applicant respectfully submits that the compounds defined as a "disease causing substance" are well known to a person skilled in the art of medicine, especially in light of the instant specification. A person skilled in the art of medicine would have no difficulty identifying and listing compounds that are "able to crystallize, precipitate, or otherwise accumulate or deposit in solid form in an animal body". Applicant further points out the term is not defined solely by its function as asserted by the Office Action. The definition begins by describing the compounds included in the term by their physical state ("solid, semisolid, paste, gel, plaque, or liquid in dissolved or undissolved form"). The compounds are further defined by the physical property of being able to "crystalize, precipitate, or otherwise accumulate or deposit in solid form in an animal body". Further included in the definition is the functional limitation of "causing or aggravating a disease process". Moreover, at least 20 specific examples of compounds are listed. Thus, Applicant respectfully requests the rejection be reconsidered and withdrawn.

Claim 40 was further rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for improperly Markush format. The claim has been canceled thereby making the objection moot. As such, Applicants respectfully request the objection be reconsidered and withdrawn.

Claims 29-34, 36-44, and 46-50 were rejected under 35 U.S.C. § 102(e) as being anticipated by Levinson *et al.* (WO 01/51919). Applicants respectfully submit that Levinson *et al.* is not available in view of the corrected priority/benefit claim (and accompanying petition to correct an unintentionally delayed claim of priority) that has been submitted herewith. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

In the previous Office Action, the previously pending claims were rejected under 35 U.S.C. § 102(e) as being unpatentable over Hol *et al.* (U.S. Patent No. 6,267,935). As the Patent Office is aware, a claim is anticipated only if each and every element as set forth in the claim is

found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). In the case of the presently claimed invention, it is respectfully submitted that Hol *et al.* fail to teach a number of the limitations found in the newly presented independent and dependent claims.

Hol *et al.* disclose "a method useful in the crystallization of proteins and other macromolecules" (see Hol *et al.*, abstract) and the "Field of the Invention" is directed to "solutions that are useful in the crystallization of molecules, especially macromolecules such as proteins" (column 1, lines 10-15). The claims of the instant invention, however, are not drawn to crystallizing proteins; rather the claims are drawn to methods of screening samples to identify conditions, compounds, or compositions that **inhibit or prevent** transitions of physical state (*e.g.*, crystallization, deposition, or precipitation (emphasis added)). Thus, the subject invention is drawn to methods of identifying conditions or composition components that provide for maintaining substances that form crystalline structures in a non-crystalline state and the methods of the subject invention are directed to the opposite end result as compared to the teachings of Hol *et al.*, namely inducing crystallization of proteins. Additionally, Applicant respectfully submits that Hol *et al.* fail to teach the selection of those processed samples that exhibit inhibition or prevention of a transition in physical state. Indeed, Hol *et al.* expressly teach that crystals are to be harvested for further analysis from those samples that exhibit a change in physical state (column 10, line 65 through column 11, line 65). Accordingly, Applicant respectfully submits that Hol *et al.* fail to anticipate the claimed invention and withdrawal of the rejection is respectfully requested.

In the previous Office Action, the previously pending claims were further rejected under 35 U.S.C. § 102(b) as being unpatentable over Leskovar *et al.* (Urolithiasis Relat. Clin. Res.). The Office Action asserts that Leskovar *et al.* teach methods of dissolving struvite, calcium oxlate and apatite calculi. The Office Action further asserts that Leskovar *et al.* teach forming an array of 1000 single calculi for testing against 44 single and combined irrigation systems. Applicant respectfully traverses.

As previously discussed, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.

Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants respectfully point out that Leskovar *et al.* do not teach a number of the limitations of the instantly claimed invention. For example, Leskovar *et al.* fail to teach: 1) preparing an array of at least 96 samples in tubes and support plates or in sample well plates; 2) the addition of a disease causing substance in liquid or dissolved form; 3) the processing of one or more samples to induce crystallization, precipitation, or deposition of a disease causing substance; 4) the analysis of the samples to detect the induction of crystallization, deposition, or precipitation; and/or 5) the selection of those processed samples that exhibit inhibition or prevention of a transition in physical state.

Leskovar *et al.* state that "our study consisted of the gravimetric analysis of more than 1000 single calculi, subdivided according to their composition as determined by X-ray diffraction and according to their size." Thus, Leskovar *et al.* did not add a disease causing substance in liquid or dissolved form; rather, Leskovar *et al.* used preformed precipitates or crystals of disease causing substances. This also appears to indicate that Leskovar *et al.* did not test an array of at least 96 samples. Leskovar *et al.* teach that they collected 1000 calculi, not that they tested 1000 calculi or that they formed and screened an array of 1000 calculi. Leskovar *et al.* further state that they weighed (gravimetric analysis) and determined the identity of the stones with X-ray diffraction and that "in total we have tested 44 single and combined irrigation systems." Leskovar *et al.* do not state that all 1000 samples were treated with the 44 irrigation systems. Table 1, for example, lists only 17 calcium oxalate stones. Table 3 lists an additional two calcium oxalate stones but does not indicate whether they were the same or different stones used in Table 1. Table 1-3 combined only list only 42 stones. Thus, Leskovar *et al.* fail to meet the limitation of screening an array of at least 96 samples. Leskovar *et al.* further do not teach or suggest the use of tubes in support plates or sample well plates and Leskovar *et al.* teach a flow rate of 1ml/min. It would appear from these teachings that the experiments have been conducted in a manner that is not compatible with either tubes in support plates or plates containing sample wells. Thus, Leskovar *et al.* do not teach or suggest and is not enabled for the use of tubes in support plates or sample well plates. Leskovar *et al.* further do not teach or suggest dispensing the disease causing substance, *e.g.*, calcium oxalate, in a liquid or dissolved form. As the Office

Action points out, the irrigation solutions of Leskovar *et al.* were used on solid stones and Leskovar *et al.* do not teach whether the stones are crystalline or amorphous. Leskovar *et al.*, further, do not teach or suggest the use of an automated distribution system. Leskovar *et al.* also do not teach or suggest the processing one or more of the samples to induce crystallization, precipitation or deposition of the disease causing substance. Leskovar *et al.* teach just the opposite. Leskovar *et al.* teach using irrigation solutions in an attempt to dissolve stones and Leskovar *et al.* further do not teach or suggest analyzing the processed samples to detect the induction of said crystallization, precipitation or deposition or the selection of those samples in which said crystallization, precipitation or deposition has not occurred.

Further, both Hol *et al.* and Leskovar *et al.* fail to teach sealing said samples; processing said samples comprising heating said samples in a sample incubation module to a temperature (T1), analyzing said samples for the presence of undissolved solids using visual analysis, cooling said samples to a final temperature (T2); tubes and support plates, and more specifically, glass tubes and metal support plates; sealing tubes with a cap; using caps that can be pierced with a standard syringe needle and fluid aspirated; an array with at least 1000 samples; using a work list for instructing an automated distribution mechanism to prepare an array of samples; piercing a cap and aspirating medium from the samples; analyzing the processed array of samples using a polarized light filter apparatus; an array comprising at least one sub-array of at least 24 samples; sample processing comprising adjusting a time of incubation; sample processing comprising adjusting a temperature; sample processing comprising adjusting a pressure; subjecting the samples to a nucleation event; sample processing comprising subjecting the samples to processing comprising ultrasound, shock waves, laser energy, or mechanical stimulation; sample processing comprising adjusting an amount of a component; sample processing comprising adding a component; sample processing comprising adjusting an amount of the medium; sample processing comprising adjusting a gas composition; screening at least about 100 samples per day; screening at least about 1000 samples per day; processing an individual sample within the array by subjecting it to methods that are different from the processing methods to which another sample is subjected, and more specifically, wherein said individual sample is subjected to processing methods comprising introducing a nucleation event or adding one or more additional

components; processing an individual sample within a sub-array by subjecting it to processing methods that are different from the processing methods to which another sample within the sub-array is subjected, and more specifically wherein said individual sample is subjected to processing methods comprising introducing a nucleation event or adding one or more additional components; processing an individual sub-array by subjecting it to processing methods that are different from the processing methods to which another sub-array is subjected, and more specifically, wherein said individual sub-array is subjected to processing methods comprising introducing a nucleation event or adding one or more additional components; wherein one or more samples differ from one or more other samples with respect to the amount of the medium; wherein the thermodynamic driving force for crystal nucleation and growth is controlled by the concentration of components, by the identities of components or by temperature; analyzing samples using machine vision technology, video-optical microscopy, image analysis, polarized light analysis, near field scanning optical microscopy, far field scanning optical microscopy, atomic-force microscopy, micro-thermal analysis, infrared spectroscopy, near infrared spectroscopy, Raman spectroscopy, NMR, neutron diffraction, powder x-ray diffraction, light microscopy, second harmonic generation, electron microscopy or an *in vitro* assay. Accordingly, reconsideration and withdrawal of the rejections is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

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Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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FCE/ehm
Attachments: Petition to Accept an Unintentionally Delayed Claim of Priority
Copy of Newly Executed Declaration (37 CFR §1.63) and Power of Attorney

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